Local Information:

La Fonda Hotel

La Pasada Hotel

Audio/Video

Talk Materials

Fall 2003

ICAM Workshop

Physics of Neural Tissue

November 2 - November 6, 2003

Organizers:

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Schedule | Participants | Abstracts

WORKSHOP SCHEDULE				
Sunday	Monday	Tuesday	Wednesday	Thursday
Sunday, November 2, 2003				
6:00	Registration			
6:00 - 7:30	Reception	La Fonda		

Monday, November 3, 2003		
7:30-8:45	**Breakfast**	La Fonda
8:45-9:00	**David Pines** LANL	Opening address
Optical properties of tissue		
9:00-9:25	**David Kleinfeld** UCSD	
9:25-9:35	Discussion	
9:35-10:00	**David Rector** U. Washington	Investigations of Neural Mechanisms of Fast Light Scattering Responses
10:00-10:10	Discussion	
10:10-10:40	**Coffee break**	
10:40-11:05	**David Boas** Harvard U./MGH	
11:05-11:15	Discussion	
11:15-11:40	**Warren S. Warren** Princeton U.	Exploiting Novel Brain Contrast with MRI and Femtosecond Laser Imaging
11:40-11:50	Discussion	
11:50-12:15	**Bruce Rosen** Harvard U./MGH	
12:15-12:25	Discussion	
12:25-1:30	**Lunch**	La Fonda
MRI contrast in neural tissue		
1:30-1:55	**Van J. Wedeen** Harvard U./MGH	
1:55-2:05	Discussion	
2:05-2:30	**Rolf Koetter** Duesseldorf	Local and global connectivity in the cerebral cortex
2:30-2:40	Discussion	
2:40-3:10	**Coffee break**	
3:10-3:35	**David S. Tuch** Harvard U./MGH	
3:35-3:45	Discussion	
3:45-4:10	**Gregory Sorensen** Harvard U./MGH	
4:10-4:20	Discussion	
4:20-4:45	**Daniel A. Gorelick** Johns Hopkins U.	
4:45-4:55	Discussion	
No special events		
Tuesday, November 4, 2003		
7:30-9:00	**Breakfast**	La Fonda
Diffusion in tissue		
9:00-9:25	**Charles Nicholson** NYU	Diffusion measurements reveal geometry of brain extracellular space
9:25-9:35	Discussion	

9:35-10:00	**Stephen J. Blackband** U. Florida	Can MR Diffusion Measurements of Tissues Provide Reliable Information on Tissue Microstructure?
10:00-10:10	Discussion	
10:10-10:40	**Coffee break**	
10:40-11:05	**Greg Stanisz** Harvard U./MGH	
11:05-11:15	Discussion	
11:15-11:40	**Pabitra Sen** Schlumberger-Doll Research	Time-dependent diffusion coefficient as a probe of the permeability of the pore wall
11:40-11:50	Discussion	
11:50-12:25		
12:25-1:30	**Lunch**	*La Fonda*
Tissue energetics		
1:30-1:55	**Geoffrey West** LANL/SFI	
1:55-2:05	Discussion	
2:05-2:30	**Lynn Hlatky** Dana Farber/BWH	
2:30-2:40	Discussion	
2:40-3:10	**Coffee break**	
3:10-3:35	**Mark Henkelman** U. Toronto	Neural Tissue as a Complex Adaptive Material: To what degree is the gross structure under genetic control?
3:35-3:45	Discussion	
3:45-4:10	**Richard B. Buxton** UCSD	A thermodynamic hypothesis for the regulation of brain energy metabolism and the basis of fMRI
4:10-4:20	Discussion	
4:20-5:10	**Salvatore Torquato** Princeton U.	The Brain as a Random Heterogeneous Material + Tutorial
5:10 - 5:30	Discussion	
6:30	**Banquet**	La Fonda
Wednesday, November 5, 2003		
7:30-8:45	**Breakfast**	La Fonda
8:45-9:00		Opening address
From neural networks to imaging		
9:00-9:25	**John S. George** LANL	
9:25-9:35	Discussion	
9:35-10:00	**Anders Dale** UCSD/MGH	
10:00-10:10	Discussion	
10:10-10:40	**Coffee break**	

10:40-11:05	**Eric Halgren** Harvard U./MGH	Neurophysiology of large-scale integrative processes in the human brain
11:05-11:15	Discussion	
11:15-11:40	**Krastan B. Blagoev** LANL/MGH	
11:40-11:50	Discussion	
11:50-12:15	**Peter Basser** **NIH**	
12:25-1:30	**Lunch**	La Fonda
Tissue response functions		
1:30-1:55	**Yoshio C. Okada** UNM	
1:55-2:05	Discussion	
2:05-2:30	**Victor Jirsa** Florida Atlantic U.	Connectivity and Dynamics of Neural Information Processing
2:30-2:40	Discussion	
2:40-3:10	**Coffee break**	
3:10-3:55		
3:55-4:05	Discussion	
4:05-4:30	Closing Discussion	
No special events		

Thursday, November 6, 2003

Departure

Participants

Abstracts

Stephen J. Blackband

Can MR Diffusion Measurements of Tissues Provide Reliable Information on Tissue Microstructure?

Stephen J. Blackband, Peter E. Thelwall, Samuel C. Grant,

Timothy M. Shepherd, Greg Stanisz.

Universities of Florida and Toronto.

There has been considerable interest in the measurement of multicomponent diffusion-weighted MR signals in biological tissues because water diffusion is influenced by structures significantly smaller than the resolution of MR images. However, interpretation of water diffusion data is difficult because tissue is heterogeneous and complex. Further, water diffusion signals often have low signal-to-noise ratios (SNR). MRI technology continues to improve the SNR available, yet it remains unlikely that studies in living animals or human patients will provide sufficient information to interpret compartmentation in biological tissues. Instead, detailed water diffusion studies in tissue models can provide critical insights into in vivo tissue microstructure. Innovative mathematical and physical

		models can be developed to explain the biophysical origins of diffusion MRI contrast. Experimental data from perfused rat brain slices, isolated Aplysia neurons and a simplified erythrocyte ghosts tissue model demonstrate that a wide range of approaches may be used to elucidate the origins of water diffusion. These studies show that the situation is complex even within individual cells, which exhibit multicomponent water diffusion within the cytoplasm. Present attempts to relate diffusion MRI signals to tissue microstructure will be discussed, but we have yet to comprehend the full impact of the unique information about cellular and subcellular organization from diffusion MRI experiments. A multi-modality approach to augment present MRI studies may be required to correlate diffusion MRI data with tissue microstructure.
	Richard B. Buxton	**"A thermodynamic hypothesis for the regulation of brain energy metabolism** **and the basis of fMRI"** **Richard B. Buxton** **University of California, San Diego** Functional neuroimaging techniques provide a powerful tool for investigating the working brain through the detection of changes in cerebral blood flow (CBF) and energy metabolism. However, the link between neural activity and energy metabolism, and even the primary biological functions served by CBF regulation, are still poorly understood. Calculations of the transport kinetics of O_2 and CO_2 between blood and brain suggest that experimental observations of CBF response to changes in neural activation, inspired CO_2, and inspired O_2 can be quantitatively explained by a simple principle: maintenance of the concentration ratio $[O_2]/[CO_2]$ at the mitochondria. A possible explanation is that this ratio is maintained in order to preserve the thermodynamic free energy (elta(G)) supplied by oxidative metabolism of glucose. This thermodynamic hypothesis focuses on the work performed by a mitochondrion on the surrounding cytosolic environment: the net conversion of one pyruvate and three O_2 molecules to three CO_2 molecules. A key model parameter that governs the behavior of the system is the diffusivity of O_2 from blood to brain. With a value of diffusivity for the brain chosen to yield cytosolic pO_2 values consistent with experimental data, the modeling predicts that the oxygen extraction fraction *E* must decrease with increased oxygen metabolic rate, with the change in CBF twice as large as the change in the cerebral metabolic

		rate of oxygen ($CMRO_2$), in good accord with recent data. This imbalance of the CBF and $CMRO_2$ changes with activation, and the resulting increase in blood oxygenation, is the source of the signal change measured with functional MRI (fMRI). Preserving the same ratio $[O_2]/[CO_2]$, but increasing the O_2 diffusivity, produces a behavior in which E stays approximately constant at a value of about 75% as oxygen metabolic rate is increased. This latter behavior is consistent with experimental observations in the heart, where the diffusivity of O_2 is expected to be higher due to a larger capillary density and possibly diffusive O_2 transport by myoglobin. Extending this thermodynamic hypothesis to include the mitochondrial conversion of NADH produced by glycolysis back to NAD^+ (through the malate/aspartate shuttle) suggests that the lactate concentration serves as an index of a favorable balance of concentrations of pyruvate, NADH and NAD^+ that helps to maintain the Delta(G) of oxidative metabolism. By this hypothesis, the formation of lactate is not necessarily a sign of oxygen deficiency and a switch from oxidative metabolism to glycolysis for energy generation, and may explain observations of lactate production under aerobic conditions.
	Eric Halgren	"Neurophysiology of large-scale integrative processes in the human brain" The talk would speak about how cognitive integration is visible at multiple scales from non-invasive fMRI (functional Magnetic Resonance Imaging) and MEG (magnetoencephalography) to invasive microelectrode arrays. The problem of multiple nested inverse/forward problems will be broached
	Mark Henkelman	**Neural Tissue as a Complex Adaptive Material:** **To what degree is the gross structure under genetic control?** **R.M. Henkelman, J.G. Sled, N. Kovacevic, N. Lifshitz, J. Chen** The completion of the mouse genetic sequence and the capability to manipulate that sequence combined with sophisticated three-dimensional imaging tools enables a new level of inquiry into the way genes give rise to structural patterning. The brain is probably the most complex organ in the biological domain in terms of both its anatomical structure but more importantly its function. It is currently believed that brains self assemble under the informatic control of approximately 30,000 genes. It is a major question to ask how this happens. Three-dimensional magnetic resonance (MR) images of genetically identical mouse brains have been acquired by us

		at 60 microns resolution. The data sets have been aligned by affine and non linear co-registrations into an average atlas showing very clear anatomical definition. The average root mean square displacement of any point in the brain to its corresponding atlas location is less than 50 microns, consistent with very high level of genetic control over structural anatomy. Thus, it is a powerful way to identify structural changes that arise with a change in the underlying genetics. When we image the three-dimensional vascular structure using micro computed tomography (CT), however, a different picture emerges. The patterning of major blood vessels is readily recognizable, but as the arbourization branches down to the capillaries, strict control of the architecture is lost. Comparative vascular architecture will be shown for brain (and other organs) and the nature of genetic control of these structures will be discussed.	
	Victor Jirsa	Connectivity and Dynamics of Neural Information Processing Viktor Jirsa Florida Atlantic University We discuss how changes in the connectivity of a neural network affect the spatiotemporal network dynamics qualitatively. The three major criteria of comparison are, first, the local dynamics at the network nodes which includes fixed point dynamics, oscillatory and chaotic dynamics; second, the presence of time delays via propagation along connecting pathways and, third, the properties of the connectivity matrix such as its statistics, symmetry and translational invariance. Since the connection topology changes when anatomical scales are traversed, so will the corresponding network dynamics change. As a consequence different types of networks are encountered on different levels of neural organization. Experimental examples are provided from the domain of multisensory integration and brain imaging (fMRI and EEG).	
	Rolf Koetter	**Rolf Koetter** **Duesseldorf University** I will present and discuss some properties of local connectivity (microcircuits) and global connectivity (association fibres) in the mammalian cerebral cortex. Starting points for a discussion could be: How do the connectional properties scale? How can we speed up the delineation of the brain's wiring? How do cytoarchitectonics relate to connectivity? What does connectivity tell us about computations?	
	Charles Nicholson	**Diffusion measurements reveal geometry of brain extracellular space** Charles Nicholson Dept. Physiology & Neuroscience, New York University School of Medicine, New York. The structure of the extracellular space (ECS) of the brain	

		resembles the water phase of a foam and can be thought of as a well-connected porous medium. The ECS is a conduit for molecular signals (volume transmission) and for essential metabolites. Diffusing molecules execute random movements and collide with membranes, affecting their concentration distribution. By measuring this distribution, the volume fraction (alpha) and the tortuosity (lambda) can be estimated. Volume fraction (porosity) indicates the relative amount of ECS while tortuosity is defined as the square root of the ratio of the effective diffusion coefficient in a free medium to that in brain and measures hindrance of cellular obstructions. Early diffusion measurements used radiotracers but more recently our laboratory has used a point source paradigm. Molecules are released from a micropipette and the resulting concentration around the source is measured. When the released molecule is tetramethylammonium (TMA^+, M_r = 74), the concentration is measured with an ion-selective microelectrode; when fluorescent macromolecules are used the concentration is determined with integrative optical imaging. The results accurately fit appropriate solutions of the classical diffusion equation with the addition of a clearance term in some cases. Diffusion measurements with TMA^+ show that alpha ~ 0.2 and lambda ~ 1.6, although some brain regions are anisotropic. Molecules > 10,000 M_r show more hindrance, but globular molecules of 70, 000 M_r (e.g. dextrans or albumins) can move through the ECS and some flexible polymers as large as 1,000,000 M_r are also able to migrate. In pathophysiological states, ☐ and ☐ change, for example in severe ischemia alpha = 0.04 and lambda = 2.2. Our recent Monte Carlo simulation has revealed that an extracellular space formed by packing a variety of convex model cells cannot generate a tortuosity greater than 1.225 so some other factor must be at work in the brain. This might be a viscous extracellular matrix or it may be that the real extracellular space contains a significant number of dead-end pores. Our experimental and theoretical work favors the dead-space explanation. Supported by NIH Grant NS 28642. Reviews Nicholson, C. & Syková, E. Extracellular space structure revealed by diffusion analysis. Trends in Neurosci. 21 (1998) 207-215. Nicholson, C. Diffusion and related transport mechanisms in brain tissue. Rep. Prog. Physics 64 (2001) 815-884.	
	David M. Rector	Investigations of Neural Mechanisms of Fast Light Scattering Responses David M. Rector Dept. VCAPP, Washington State University, Pullman, WA	

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Significant effort has been invested in techniques that use light to acquire images of brain activity. Most of this effort has been devoted to visualizing comparatively slow processes such as the changes in blood flow, volume and oxygenation that accompany metabolic activation of neural tissue. Changes in light absorbance associated with metabolic and hemodynamic processes are robust and relatively easy to obtain non-invasively, but spatial and temporal resolution is limited by the anatomy and physiological regulation of cerebral perfusion.

We have been investigating neural mechanisms associated with fast changes in scattered light that are highly correlated in space and time with electrophysiological processes within nerves. Investigators have recorded fast light scattering signals from isolated nerves for more than half a century, but we have only recently been able record and image such fast signals within intact tissue. Using signal decomposition techniques, we identified four components of the optical response associated with electrical stimulation of the rat dorsal medulla. These included two fast components related to electrical events, and two slower components related to hemodynamic processes. We have observed very fast optical changes in rat somatosensory cortex that appear to be directly related to the evoked electrical response and to a fast (200-600 Hz) oscillation that often accompanies the evoked response. <!-- @page { margin: 2cm } P { margin-bottom: 0.21cm } --> Such in-vivo signals are small compared to noise, often requiring 100 to 1000 averages to see clearly. The required averaging precludes studies of the dynamic properties of neural activation in single passes. We are investigating the biophysical mechanisms of the fast optical changes in order to develop new strategies to improve optical contrast and signal-to-noise for in-vivo and non-invasive applications.

Polarized light birefringence measurements in isolated lobster nerve show a 10 to 100 fold increase in signal contrast compared to large angle scattering measurements. The time courses of the two signals are different in detail, suggesting that biophysical mechanisms may also be different. We have shown that the electrical activation of isolated nerve is associated with a fast transient swelling response, perhaps due to the movement of water accompanying the movement of ions that underlies the electrophysiological response. We are exploring a number of other cellular mechanisms proposed for fast optical changes, in order to better interpret the results of experimental work and to optimize the neuroscience application of these methods.

Optical techniques have great potential for dynamic functional neuroimaging. Optical imaging techniques also enhance our understanding of the tissue responses that form the basis of conventional functional MRI as well as emerging methods based on diffusion imaging. Although much work remains to optimize spatial reconstruction algorithms for non-invasive techniques and to characterize mechanisms and optimize methods for imaging fast optical changes, birefringence OCT and frequency domain optical techniques show promise for probing deep into tissue and

	may pave the way for the next generation of functional imaging devices.
Pabitra Sen	Time-dependent diffusion coefficient as a probe of the permeability of the pore wall **Pabitra N. Sen** Schlumberger-Doll Research, Ridgefield, Connecticut 06877-4108 Received 6 May 2003; accepted 28 July 2003! To appear in JOURNAL OF CHEMICAL PHYSICS VOLUME 119, NUMBER 16 22 OCTOBER 2003 The time dependence of the mean-square displacement ~or equivalently of the diffusion coefficient! in the presence of a permeable barrier can be used as a probe of the surface-to-volume ratio and permeability of a membrane. An exact, universal, short-time asymptotics in a pack of cells, assuming that the surfaces are locally smooth, shows that the effects of nonzero permeability appear as a correction to the diffusion coefficient that is linear in time, where as the surface-to-volume ratio enters as a square root in time. The NMR data on erthrocytes show that the effect of permeability can be significant within the time scales of measurement and hence permeability is deducible from the data. The long-time behavior given previously (Proc Natl. Acad. Sci. USA 92, 1229 ~1994) is augmented by giving a nonuniversal form that includes the rate of approach to this limit.
Salvatore Torquato	**The Brain as a Random Heterogeneous Material** Salvatore Torquato Dept. of Chemistry and Princeton Materials Institute Princeton University, Princeton, N.J. 08544 USA torquato@princeton.edu http://cherrypit.princeton.edu The brain can viewed as a random heterogeneous material, i.e., a material that is composed of randomly arranged domains of different materials (phases). I briefly review the connection between the effective properties (e.g., diffusion tensor, effective conductivity tensor, NMR lifetimes, elastic moduli, fluid permeability tensor) of a heterogeneous material and microstructural descriptors. The latter take the form of n-point statistical correlation functions, and embody not only statistical geometric information but topological properties about the material. This is achieved by marrying continuum-field theories with statistical-mechanical

techniques [1]. I also discuss cross-property relations that enable one to predict one effective property of a heterogeneous material given a measurement of a different effective property. Finally, I close with a brief description of a computer simulation that models the growth of a brain tumor.

1. S. Torquato, "Random Heterogeneous Materials: Microstructure and Macroscopic Properties," (Springer-Verlag, New York, 2002).